EVIDENCE-BASED CASE REVIEWS

Acute otitis media

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A 3-year-old girl is brought to your office by her mother because she has a fever and complains that her ear hurts. She has no significant medical history. The child is not pleased to be in the physician's office and has been crying. Her mother explains that she developed a "cold" about 3 days ago with sniffles. Her temperature is 37.8°C (100°F), and the rest of the physical examination is completed with some difficulty. The only abnormalities are slight redness of the throat, a nose full of thick green mucus, and injected tympanic membranes. You wonder what findings other than red tympanic membranes should lead you to diagnose otitis media and also consider the recent controversy about whether to treat acute otitis media (AOM) with antibiotics.

Summary points

- Symptoms of acute otitis media are so nonspecific that they are largely unhelpful in making a diagnosis
- Earache is the only symptom with sufficient positive predictive value to be useful in diagnosing acute otitis media
- Among the signs of acute otitis media, cloudiness and bulging of the tympanic membrane help rule in the diagnosis, and the absence of impaired mobility helps rule it out
- Treatment with antibiotics reduces the pain of acute otitis media after (but not before) day 1 of treatment in only 1 out of 17 children, but a similar proportion has antibiotic-related side effects
- Antibiotic therapy has no important effect on hearing loss
- The basis for deciding whether to administer antibiotics should include not only this evidence but also parental values

BACKGROUND

Acute otitis media is a disease of infancy and early childhood defined by the presence of inflammation and fluid in the middle ear and accompanied by at least 1 sign of acute illness.[1] In studies in which the content of the middle ear cavity was examined during attacks of AOM, both bacterial and viral pathogens were found.[2-6] However, 12 different case series failed to identify any causative infectious agent in the middle ear fluid of 28% to 62% of affected children.[7] In the United States, the United Kingdom, and Australasia, standard practice is to start antibiotic treatment promptly on diagnosis.[8] This is not the norm in parts of continental Europe, particularly the Low Countries and Scandinavia.[9] Some have argued that infective or inflammatory fluid in a confined space constitutes an abscess and that, therefore, a surgical approach (tympanocentesis) is necessary. Another view altogether suggests that AOM is a "self-limiting" (spontaneously remitting) illness,[10] the normal resolution of which is fast enough to obviate the need for any treatment.[9,11]

Table 1 summarizes the incidence rates and cumulative incidences reported in 8 appropriately designed epidemiologic studies.[12-19] Despite differences in study design, diagnostic criteria, and study population, the incidence rates were remarkably similar among the studies. In most of the studies, the peak incidence occurred during the second 6 months of life.[12-14,16,18] However, 2 studies found the incidence was greatest after 12 months, either in the 12- to 24-month period[15] or in the third year of life.[19] Several studies also found that male children have a significantly higher rate of first occurrence of AOM and of recurrence.[12,13] Overall, about 17% to 30% of children have 2 or more episodes of AOM during the first year of life.[13,17] The fact that 50% of children had had at least 1 episode of AOM before 3 years of age and 75% before the age of 10 years demonstrates how common this disorder is.[12]

Several clinical questions arise from the scenario. What symptoms and signs accurately predict the diagnosis of AOM in children? Does antibiotic treatment shorten the duration of illness or change the likelihood of complications? You wish to use an evidence-based approach, so you frame your questions to maximize the yield of a search and look first for high-quality systematic reviews and evidence-based practice guidelines to answer your questions.

SEARCH STRATEGIES

For diagnostic evidence, you decide to search for studies that examine the following:

- The frequency and likelihood ratios (LRs) of various associated symptoms: you search MEDLINE using the search terms *acute otitis media* AND (*signs OR symptoms*) and *acute otitis media* AND (*earache OR pain OR fever OR cough OR rhinitis*)
- The predictive ability of various signs of AOM: you search MEDLINE using the search terms *acute otitis*

The previous articles in this series are available on our web site.

Table 1 *Incidence of acute otitis media in population studies**

Study	No. of children	Follow-up period, mo	Age of children, yr	Age at peak incidence (%), mo	Overall incidence, % Incident rate/yr	Cumulative incidence
Pukander et al, 1982[12]	37,570	12	0–15	6–11 (76)	17	—
Sipila et al, 1987[13]	1,642	18	0–1.5	10	—	45 by 1 yr
Alho et al, 1991[14]	2,512	24	0–2	12	—	42 by 1 yr
Joki-Erkkila et al, 1998[15]†	2,921	12	0–10	12–24 (37)	19	—
Joki-Erkkila et al, 1998[15]‡	2,611	12	0–10	12–24 (63)	32	—
Aniansson et al, 1994[16]	400	12	0–1	8–12 (62)	—	21 by 1 yr
Howie and Schwartz, 1983[17]	4,602§	12	0–17	0–12 (21)	18	—
Teele et al, 1989[18]	498	84	0–7	6–12 (56)	—	62 by 1 yr
Ross et al, 1998[19]	334	12	0–3	24–36 (31)	22	—

*A dash indicates that incidence data were not given.
†1978 data.
‡1994 data.
§Office visits.

media AND (*clinical signs OR diagnosis OR otoscop** *OR pneumatic otoscop** *OR pneumotoscop** *OR tympanic membrane*), with the asterisk as a "wildcard" that searches for terms containing the word fragment preceding the asterisk

For evidence of effectiveness, you search for summaries in *Clinical Evidence*, the Cochrane Library, in *Best Evidence*, and in MEDLINE. You find 1 chapter on AOM in the child health section of *Clinical Evidence*. The Cochrane Library (2001, issue 3) reveals 25 completed reviews and 9 protocols. One completed review directly addresses the question of antibiotic treatment of AOM in children.[20] The Database of Reviews of Effectiveness lists 3 more reviews that address the effectiveness of antibiotic therapy.[8,21,22] A search of MEDLINE in which *acute otitis media* is used as a major subject heading and *meta-analysis* as a text word nets no additional studies.

DIAGNOSIS

What are the symptoms of AOM?

What specific symptoms are most helpful to your making an accurate diagnosis of AOM? Some common signs and symptoms, such as pulling of the ear and erythema of the tympanic membrane, may be found in children who do not have AOM,[23] and symptoms such as earache and fever—"classic" findings of AOM—are sometimes absent. Your search yields 8 studies in which the frequency of symptoms in children with AOM is reported.[18,19,24-29] After critical appraisal, you base your evaluation on the 5 studies in which symptoms are compared with an independently evaluated reference standard for the diagnosis, and thus, these studies appear the most likely to have valid results.[24-26,28,29]

Table 2 summarizes the findings from these studies. Earache is an inconsistent finding, with a reported frequency between 21% and 83%. In a prospective Finnish cohort study, earache was about 7 times more likely to be elicited from a child with AOM than from a child who did not have AOM (LR, 7.3).[26] However, a more important finding is that 40% (48/121) of the children with AOM in this study had no apparent earache (LR for no earache, 0.4). This means that earache is a more useful symptom for "ruling in" the diagnosis of AOM than for ruling it out.

Cough and rhinitis are relatively common symptoms among children with otitis media because AOM is associated with upper respiratory tract infection in 76% of cases.[30] Unfortunately, they are also nonspecific symptoms—equally likely to be found in a child with AOM as in a child without it (LR, 1.0).[26]

Fever, like earache, is also an inconsistent finding in AOM, occurring in 21% (70/335) to 84% (165/197) of patients.[24,28] In 1 study, fever was an equally common finding among children with AOM and age-matched controls.[28] In another study, the presence of fever actually decreased the likelihood of having AOM, with positive and negative LRs of 0.9 and 1.3, respectively.[26]

In neither of 2 studies in which the frequency of vomiting and diarrhea was addressed were these symptoms more common in children with AOM than in children with other acute illnesses.[28,29]

In summary, AOM cannot be reliably differentiated

Table 2 *Prevalence of associated symptoms in children with otitis media*

Study	Children with acute otitis media (based on signs) with the symptom, %							
	Earache	Ear pulling	Irritability	Cough	Catarrh or rhinitis	Fever	Vomiting	Diarrhea
Hayden and Schwartz, 1985[24]	83	NS	NS	NS	NS	21	NS	NS
Kontiokari et al, 1998[25]	59	NS	39	NS	50	42	NS	NS
Heikkinen and Ruuskanen, 1995[26]	60	NS	NS	83	96	69	NS	NS
Uhari et al, 1995[28]	21	NS	NS	71	67	84	26	18
Niemala et al, 1994[29]	54	42	55	47	24	40	11	8
Range	21–83	42	39–55	47–83	24–96	21–84	11–26	8–18

NS = not stated.

from upper respiratory tract infection on the basis of symptoms alone. Earache is the only symptom that is more likely to be found in children with AOM than in those without the illness.

What signs are characteristic of AOM?

To address the signs of AOM, you identify a number of studies, only 1 of which actually provides sensitivity, specificity, and predictive values for the various tympanic membrane changes seen in AOM.[31] In this large Finnish study, 2,911 unselected children were examined, half by an otolaryngologist and half by a pediatrician in 2 different geographic areas. When middle ear effusion was suspected, myringotomy was performed to confirm its presence. Restricting the use of confirmatory myringotomy to only those children who were suspected of having middle ear effusion on otoscopy may lead to "verification bias" (a distortion of the properties of a diagnostic test that occurs when its result influences whether patients undergo confirmation by the "gold" or reference standard). The effect would be to improve both sensitivity and specificity. In this case, because of the high proportion (20%) of myringotomies that yielded negative results, it is unlikely that many children with middle ear effusion were missed by only verifying the positive results. Table 3 summarizes the findings from this study.[31] Because predictive values are dependent on both the accuracy of the test and the pretest probability, they have been replaced by LRs, which mainly reflect the accuracy of the test.

Mark Clarke/SPL

Earache: the only symptom valuable in diagnosing AOM

As is evident in table 3, observed redness of the tympanic membrane has poor sensitivity in AOM because it is seen in about 14% to 27% of patients.[31] The presence of redness predicted only about half of the cases in which acute symptoms occurred. In children examined by the otolaryngologist, a red tympanic membrane was just as likely to be found in children with AOM as in children without it.

A cloudy or opacified tympanic membrane is a strong predictor of AOM. The high LRs for the presence of this sign (16.2 and 6.7) confirm that it is much more likely to be found in children with AOM, although previous episodes of AOM and glue ear can render the tympanic membrane opaque. In addition, very young infants (younger than 4 months) may have decreased translucence in the absence of disease.[32]

Bulging of the membrane shows the highest LRs for a positive result (20.3 and 13.7), indicating that it is far more likely to be present in children with AOM than in those without AOM. Unfortunately, the absence of bulging (LR for a negative test result, 0.40 and 0.61) is much less helpful in excluding AOM.

Impaired tympanic membrane mobility indicates an increased likelihood of AOM (LR for a positive test result, 4.7 and 3.4), but it is most useful in ruling out AOM when it is absent (LR for a negative test result, 0.03 and 0.08).

Based on the findings in this study, it would appear that redness and retraction of the tympanic membrane (LRs close to 1.0) are relatively poor signs on which to base a diagnosis.[31] The presence of cloudiness and bulging (with high LRs when present) helps to rule in the diag-

Table 3 *Sensitivity (Sens), specificity (Spec), positive predictive values, and likelihood ratios of otoscopic findings among children with acute symptoms for middle ear effusion**

Tympanic membrane findings	Children examined by otolaryngologist				Children examined by pediatrician			
	Sens, %	Spec, %	LR+	LR −	Sens, %	Spec, %	LR+	LR −
Red	18	84	1.1	0.98	27	84	1.7	0.87
Distinctly red†	14	91	1.6	0.95	24	92	3.0	0.83
Cloudy	81	95	16.2	0.2	67	90	6.7	0.37
Bulging	61	97	20.3	0.40	41	97	13.7	0.61
Refracted	7	91	0.8	1.02	19	88	1.6	0.92
Impaired mobility	98	79	4.7	0.03	94	72	3.4	0.08

LR+ = likelihood ratio for positive findings; LR − = likelihood ratio for negative findings.
*Data adapted from Karma et al.[31]
†Hemorrhagic or strongly or moderately red.

nosis of AOM, and normal mobility helps to rule it out. Clearly, reliance on any one sign or symptom is likely to include many false-positives and false-negatives.

What treatment is effective?

The ideal evidence for the effectiveness of a treatment comes from well-conducted randomized controlled trials, especially trials using relevant outcomes such as symptoms and complications of AOM (a shorter illness in terms of pain and deafness, later episodes of illness, and side effects from antibiotics themselves) rather than "signs." Meta-analyses of such trials that showed a homogeneous effect would represent the best possible evidence.

The chapter in *Clinical Evidence* concludes that evidence on the effectiveness of antibiotic treatment is conflicting and cites the same systematic reviews that you found in your search of the Cochrane Library.[8,20-22] One meta-analysis includes studies that more closely fulfill the strict criteria mentioned earlier and included only data relevant to patient-centered outcomes.[20]

Table 4 from this meta-analysis shows the size and direction of the effect of antibiotic treatment on AOM in children. Antibiotic treatment has no effect on pain within the first 24 hours; however, the odds of having pain at 2 to 7 days if children are given antibiotics at the initial visit are reduced by 28%. Similarly, the early use of antibiotics has no effect on the deafness of AOM at 1 month after the episode. Although there is a trend to reduced hearing loss at 3 months, this may be due to chance alone because the 95% confidence interval crosses the odds ratio of 1.0.

What complications are associated with AOM?

Randomized controlled trials and meta-analyses of randomized controlled trials answer questions about reasonably common outcomes, so some adverse events may be too rare to be picked up. The most common major complication of AOM is mastoiditis. Our selected meta-analysis refers to 2 studies that addressed mastoiditis.[20] One case series from 1954 reported an incidence of 17%.[41] If this rate still occurs in modern times, it should be evident in this meta-analysis, but only 1 case was recorded (in the antibiotic group). In another study of children aged 2 to 12 (not controlled and thus not included in the meta-analysis), only 2 children whose illness was managed without the early use of antibiotics developed mastoiditis (and were successfully treated with oral amoxicillin) out of 860 with AOM.[11] Other more serious complications of AOM (such as meningitis) occur at rates so low that even large trials cannot detect them. The number of children who must be treated to prevent such rarities would be astronomic and would be subject to rare and devastating adverse effects of orally administered antibiotics.[42]

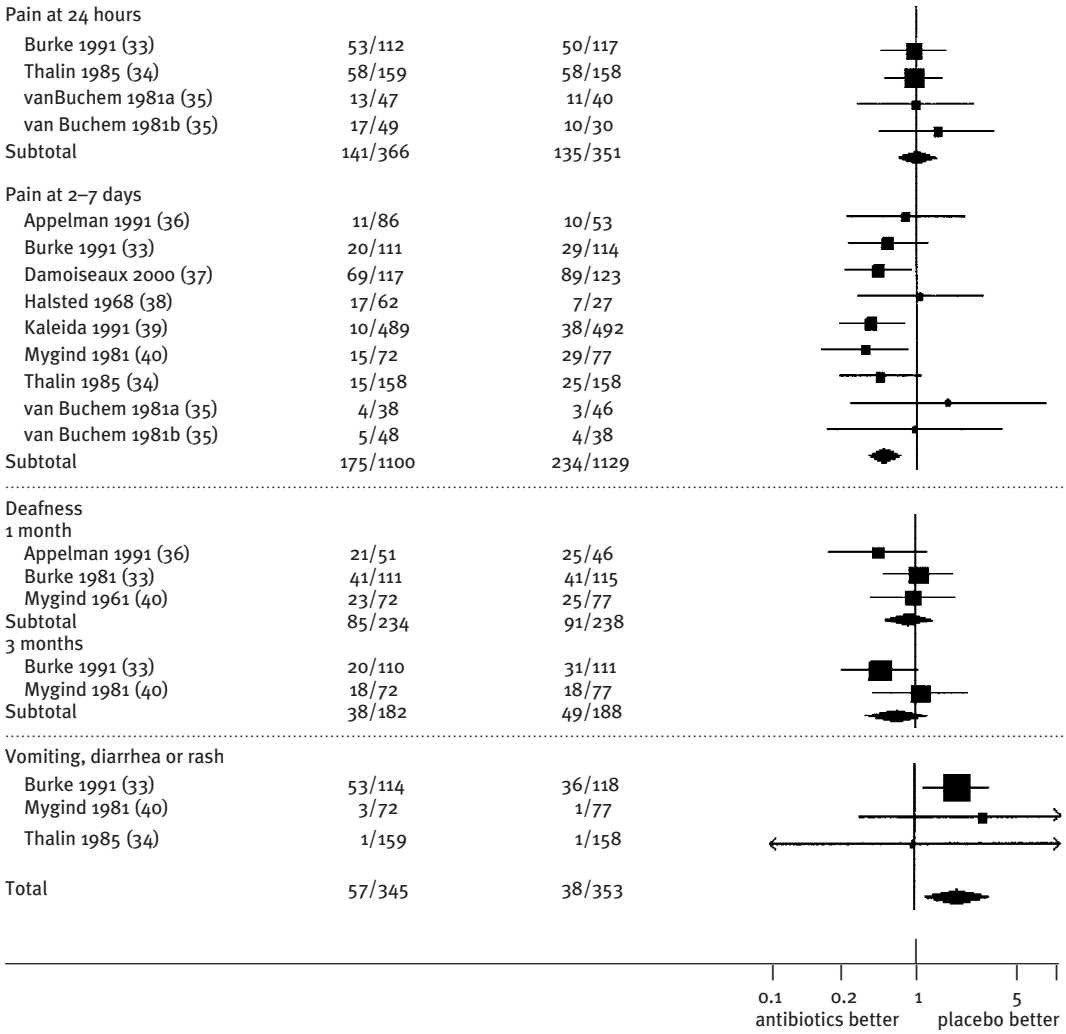
Antibiotics have side effects. The meta-analysis showed a near doubling of the chance of diarrhea, rashes, and abdominal pain: about 1 child has adverse effects for every 20 treated.

The cost of antibiotic use can be expressed in terms of the harms of treatment as well as in monetary terms. Some harms are borne by society in general, such as the development of antibiotic resistance. Antibiotics used now (even for minor, self-limiting conditions) may be unavailable for use in the future (even for serious, life-threatening conditions).

The need to consider patient preference is clear. How can you present this information to your patient's mother? The data in table 4 can be described as suggesting that treatment with antibiotics provides a relative benefit by reducing the risk of pain by 28% (95% confidence interval, 15%-38%) after day 1. However, the absolute benefit of antibiotic treatment will depend on the prevalence of

Table 4 *Summary of the evidence relating to antibiotics for acute otitis media**

Study	Expt n//N	Ctrl n/N	Peto OR (95% CI fixed)
Pain at 24 hours			
Burke 1991 (33)	53/112	50/117	
Thalin 1985 (34)	58/159	58/158	
vanBuchem 1981a (35)	13/47	11/40	
van Buchem 1981b (35)	17/49	10/30	
Subtotal	141/366	135/351	
Pain at 2–7 days			
Appelman 1991 (36)	11/86	10/53	
Burke 1991 (33)	20/111	29/114	
Damoiseaux 2000 (37)	69/117	89/123	
Halsted 1968 (38)	17/62	7/27	
Kaleida 1991 (39)	10/489	38/492	
Mygind 1981 (40)	15/72	29/77	
Thalin 1985 (34)	15/158	25/158	
van Buchem 1981a (35)	4/38	3/46	
van Buchem 1981b (35)	5/48	4/38	
Subtotal	175/1100	234/1129	
Deafness			
1 month			
Appelman 1991 (36)	21/51	25/46	
Burke 1981 (33)	41/111	41/115	
Mygind 1961 (40)	23/72	25/77	
Subtotal	85/234	91/238	
3 months			
Burke 1991 (33)	20/110	31/111	
Mygind 1981 (40)	18/72	18/77	
Subtotal	38/182	49/188	
Vomiting, diarrhea or rash			
Burke 1991 (33)	53/114	36/118	
Mygind 1981 (40)	3/72	1/77	
Thalin 1985 (34)	1/159	1/158	
Total	57/345	38/353	



*Results from each trial are represented by a black square and a horizontal line, corresponding to the point estimates and the 95% confidence intervals (95% CI) of the odds ratio (OR). The size of the black squares reflects the weight of the study. The diamond represents the combined OR with its 95% CI. The solid vertical line represents an OR of 1 and signifies no treatment effect. If the CI includes 1, then the difference between the treatment and control group is not significant at conventional levels ($P > 0.05$). Expt = experimental, Ctrl = control. From Glasziou et al.[20]

the pain and the relative benefit conferred by the antibiotics. Pain was present in only 21% of children in control groups after day 1. Therefore, the use of antibiotics will reduce the chance of children having pain from 21% to 15% (a 28% relative risk reduction). The risk difference is 6%, making the number of children a physician must treat to prevent 1 child from having pain after day 1 about 17 (100/6).

The bottom line is a choice between offering antibiotic therapy and a reduction in the chance of having pain after day 1 in 1 out of 17 children and a similar increase of side effects from the antibiotics.

Families will vary in judging whether this information indicates that the choice is worthwhile. This depends on the values that parents have for different experiences such as pain during the night for their child, the effectiveness of alternatives for pain management such as analgesics, and the complications of antibiotic use.

Based on an annual incidence rate of 0.3 (30%)[19] and an estimated duration of AOM of 2 days, this 3-year-old child has a 0.2% pre-examination probability of having AOM. Because the LR for fever is 1.0, its presence does not affect her post-test probability of AOM. Her complaint of ear pain, with an LR of 7.3,[26] increases the post-test probability to 1.5%. Her only physical finding is

redness of the tympanic membrane, which has an LR of 1.0 and, therefore, would not alter the post-test probability. If she had bulging of the tympanic membrane (LR of 20.3), the post-test probability would be increased to about 4%. (Because her ear pain and redness of the tympanic membrane are unlikely to be independent findings, we cannot use the 2 LRs in sequence). You and the child's mother discuss the possible benefits and harms of treating her presumed otitis media with antibiotics and decide to provide only analgesics for now, but you advise the mother to keep in touch in case her child's condition worsens.

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